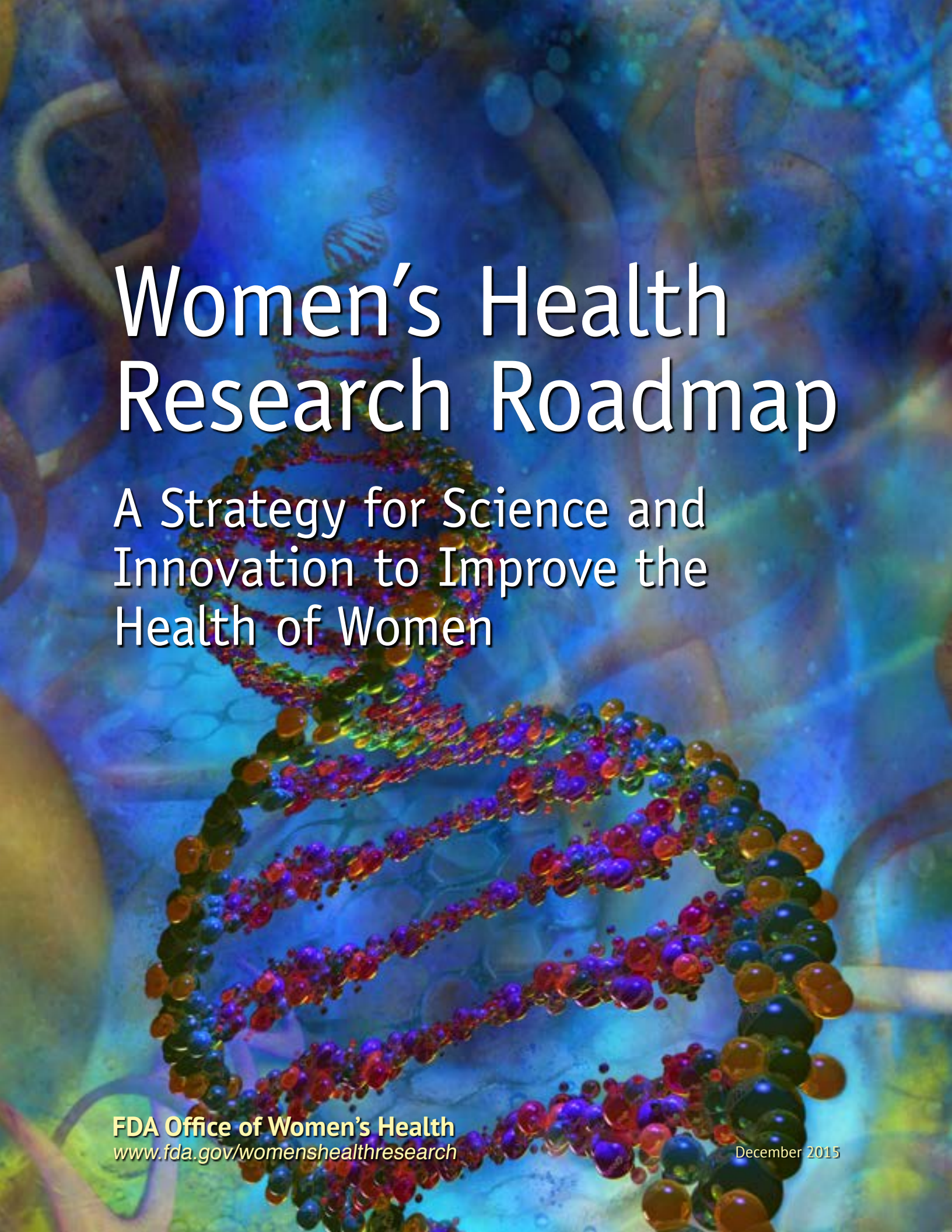


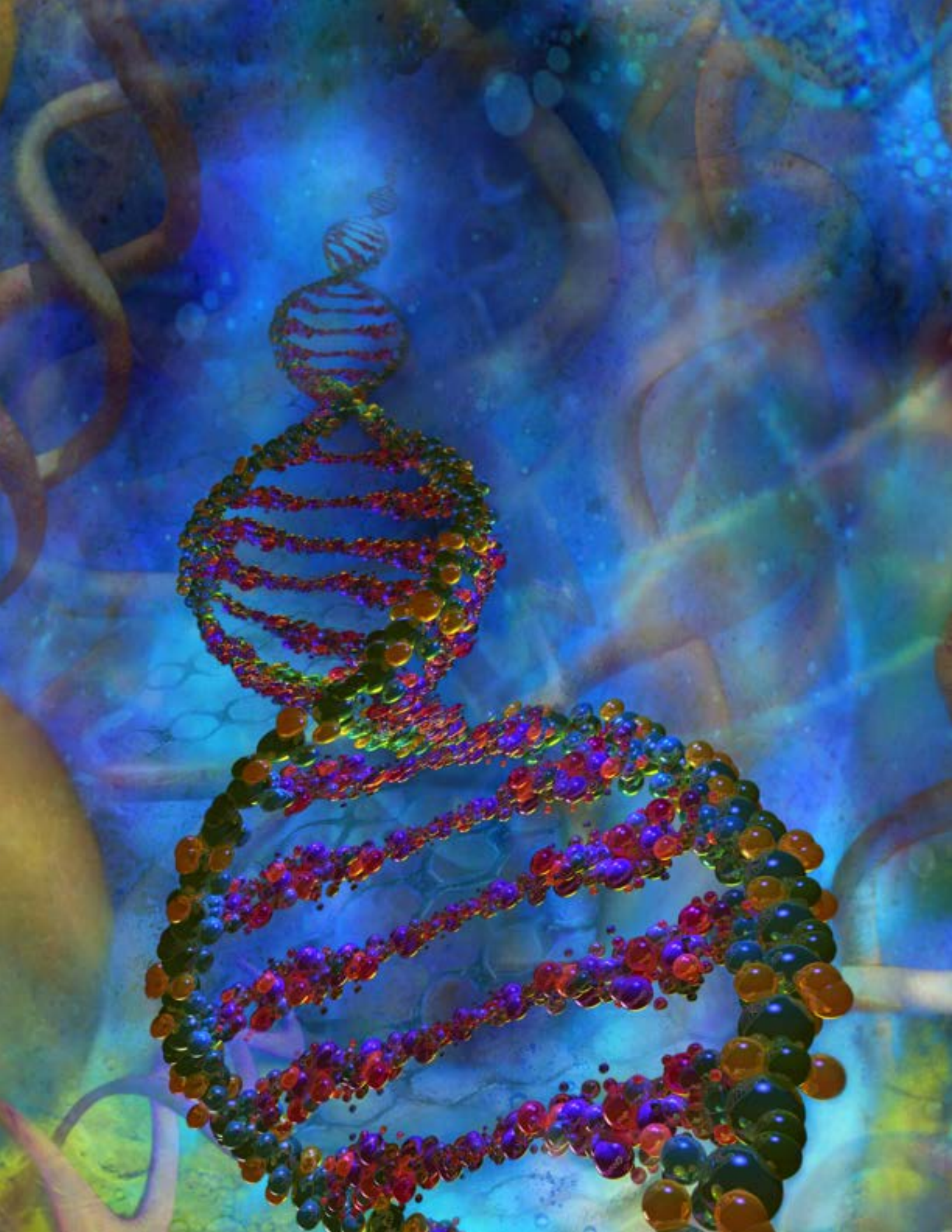
Women's Health Research Roadmap

A Strategy for Science and Innovation to Improve the Health of Women

FDA Office of Women's Health
www.fda.gov/womenshealthresearch
December 2015

Table of Contents

Women's Health Research Roadmap



Women's Health Research Roadmap

Executive Summary

The U.S. Food and Drug Administration (FDA) is a science-based, regulatory agency with the core mission of protecting the public health (see FDA Mission Statement in the Introduction).[1] The foundation of FDA's public health and consumer protection mission is *regulatory science*, the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.[2] The research under way at FDA helps FDA scientists assess the toxicity, safety, efficacy (or effectiveness), quality, and performance of the medical and other products FDA regulates. This research also contributes to advances in science and technology in general and promotes innovation in medical product development and food and cosmetic safety. FDA's research also helps alert the Agency to potential safety issues, like product contamination, and other problems that may become apparent only after a product enters the marketplace.

In 1994, FDA's Office of Women's Health (OWH) established a program to support FDA research and development activities related to advancing the science of women's health.[3] Over the past two decades, OWH has funded research projects totaling approximately $35 million.[4] These projects have addressed health issues affecting women across their lifespan, including, for example, endocrine and metabolic disorders, cardiovascular disease, breast cancer, sexually transmitted infections, and issues related to pregnancy. Results from OWH-supported research have led to safety labeling changes for some medical products, guidance for industry on product development, new evidence-based communications about FDA-regulated products used by pregnant women, and regulatory decisions related to FDA-regulated products used by women.[5]

1 See *http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/budgetreports/ucm298331.pdf*.

2 FDA's *Strategic Plan for Advancing Regulatory Science* is available at *http://www.fda.gov/scienceresearch/specialtopics/regulatoryscience/ucm267719.htm*. Accessed June 24, 2015.

3 See the OWH website at *http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/default.htm*.

4 From 1994 to 2015, OWH funded 340 research projects supporting the advancement of the science of women's health.

5 Obias-Manno D, Scott PE, Kaczmarczyk J, et al. The Food and Drug Administration, Office of Women's Health: Impact of Science on Regulatory Policy. *J Women's Health* 2007 July-Aug; 16(6)807-17, available at *http://www.ncbi.nlm.nih.gov/pubmed/17678451*. Accessed March 22, 2015.

Executive Summary

Since its inception, OWH has worked closely with FDA's centers,[6] which is where many research activities are underway. OWH has helped to expand existing research projects and foster new collaborations. OWH has also worked with other governmental agencies, academia, women's research organizations, and other stakeholders to foster and facilitate research projects and scientific forums. These combined efforts have helped to advance our understanding of women's health issues. They have furthered the development of new tools and approaches for informing FDA decisions about the harm or the safety and effectiveness of FDA-regulated products that are used not only by women, but by all Americans.

The Women's Health Research Roadmap (Roadmap), outlined in this report, builds on knowledge gained from previously funded research and is intended to assist OWH in coordinating future research activities with other FDA research programs and with external partners. The Roadmap outlines priority areas where new or enhanced research is needed. Although many critical women's health issues may warrant further examination, future OWH-funded research should focus on areas where advancements will be directly relevant to FDA as it makes regulatory decisions. The Roadmap creates strategic direction for OWH to help maximize the impact of OWH initiatives and ultimately promote optimal health for women.

Importance of Women's Health Research

Women's health research is critically important. We know that disease sometimes manifests differently in women than in men; sometimes women also respond differently to FDA-regulated products. A number of factors can influence these differences. Intrinsic factors (e.g., genetics, hormones, body size, sex-specific physiology), extrinsic factors (e.g., diet, sociocultural issues, environment), or interactions among these and other factors can play an important role in how women respond to therapies. Characteristics associated with female sex (e.g., size, age, co-morbidities, past pregnancies) may be associated with differences in the safety or effectiveness of a particular medical product.

6 FDA's centers are the (1) Center for Biologics Evaluation and Research, (2) Center for Drug Evaluation and Research, (3) Center for Devices and Radiologic Health, (4) Center for Food Safety and Applied Nutrition, (5) National Center for Toxicological Research, (6) Center for Tobacco Products, and (7) Center for Veterinary Medicine. For more on FDA centers, see *http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm2006146.htm*, accessed November 2015.

Executive Summary

Because these differences in health, disease, and treatment response can occur throughout a woman's life–and may be substantial, depending on her stage of life–a deeper analysis is needed of how regulated products work in diverse populations of women. For example, it is important to understand whether and how hormonal changes affect product performance at the onset of puberty, during the menstrual cycle, during pregnancy, and during the transition from pre-menopause, to peri-menopause, to post-menopause. We must improve our understanding of how to identify and interpret sex differences in addition to understanding how these differences might affect treatment. This is especially important, given the many evolving new technologies and scientific fields, such as nanotechnology; pharmacogenomics; stem cells; and novel imaging techniques and methods used to improve diagnosis. Advances in our understanding in these areas will contribute to FDA's ability to carefully evaluate the many innovative therapeutic products in the development pipeline.

New clinical trial and study designs could help ensure effective use of small samples and sub-population analyses. New methods, processes, and tools can help evaluate medical device designs, predict toxicity, or predict the safety and efficacy of FDA-regulated products and guide medication dosing for women. Biomarkers, patient reported outcomes,[7] and other tools are increasingly being used during medical product development and in the clinic to help understand disease, therapy, and patient response to therapy. Advances in the science of biomarkers could help improve our understanding of the molecular underpinnings of disease in women and provide the data necessary to evaluate the safety and effectiveness of medical products, leading to advances in personalized, or

7 A *patient reported outcome (PRO)* is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on a symptom or group of symptoms, on effects on a particular function or group of functions, or on a group of symptoms or functions shown to measure the severity of a health condition. PRO instruments have proved useful in assessing medical product labeling claims. See, for example, FDA guidance, available at *http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf*. Accessed June 26, 2015.

Executive Summary

precision, medicine.[8]

The information gained from this research must be clear and readily available to multiple diverse subpopulations of women to help them and their health care professionals make informed choices about the regulated products available to them. Social science research can help identify and evaluate methods for eliciting patient perspectives on disease, treatment options, and effects of treatment and for delivering information to women and determining how individual factors like sex, age, culture, and health literacy might affect consumer understanding of product labeling and other FDA communications about regulated products.

FDA is interested in any patient or population characteristics that might affect the course of a disease or condition or the toxicity, safety, or effectiveness of an FDA-regulated product available to women. The goal is not just to identify that differences exist from one subpopulation to the next. The goal is to determine when identified differences have clinically meaningful[9] effects on patient health. This information can then be used to guide clinical decisions about the optimum course of action and inform the development of better diagnostic and therapeutic products for all subpopulations of women.

By promoting collaborative research in mission critical areas, developing new tools, applying this new knowledge during FDA's review process, and strategically coordinating the findings so that they inform regulatory and policy decisions, FDA will be better positioned to foster the advancement of innovative products that promote and protect the health of all Americans.

Roadmap Development and Goal

Consistent with its mission to foster and facilitate advances in the science of women's health, in 2013 OWH launched a two-year process to develop a new research strategy, a roadmap, for determining the focus of future OWH research

8 Also known as *individualized treatment*, or *targeted therapy*, precision medicine makes use of blood tests, images of the body, or other technologies to measure individual factors called *biomarkers*. These *biomarkers* can then be used to determine who is most likely to benefit from a treatment, who is at higher risk of a side effect, or who needs a different dose. For more, see *http://blogs.fda.gov/fdavoice/index.php/2015/03/fda-continues-to-lead-in-precision-medicine/*. Accessed June 26, 2015.

9 The definition of *clinically meaningful* can vary depending on the disease or condition being considered, the therapy under consideration, and the goal of therapy. Generally, however, it can be understood to mean a measurable medical or statistical benefit to a patient or subgroup, respectively, in a given situation.

Executive Summary

activities. Based on information gained through this process, OWH developed a list of proposed research areas where new or enhanced research is considered essential to OWH's and FDA's mission.

The goal of the Roadmap is to provide a framework for continuing to integrate women's health science into all of FDA's research activities. OWH will use the Roadmap to make effective and efficient funding decisions that are aligned with FDA's research priorities. The Roadmap strengthens OWH's previous research efforts by publicly presenting a science-based framework that aligns directly with FDA's priorities and strategic goals[10] and within which OWH can make effective and efficient funding decisions. Moreover, the Roadmap will serve as a catalyst for future collaborations and other efforts related to protecting and advancing the health of women. Finally, stakeholders external to FDA will find the Roadmap useful as they seek OWH collaborative opportunities.

FDA is interested in patient or population characteristics that might influence the presentation, course, or outcome of a disease, thus affecting the toxicity or the safety, effectiveness, and security of an FDA-regulated product that is used by women. The task is not just to identify that differences exist from one subpopulation to the next. The task is to identify when sex differences have *clinically meaningful*[11] effects on patient health. To develop better diagnostic and therapeutic products for all subpopulations of women, it is important to examine more closely the possible roles sex differences play.

The process of developing the Roadmap was under way before FDA issued its report *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*. However, because it is such an important component of FDA activities in this area, the Roadmap was subsequently designated a key FDA commitment in the August 2014 *Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data*, referred to in

10 FDA's regulatory science priorities can be found at *http://www.fda.gov/scienceresearch/specialtopics/regulatoryscience/ucm267719.htm*, accessed June 28, 2015.

11 The definition of *clinically meaningful* can vary depending on the disease or condition being considered, the therapy under consideration, and the goal of therapy. Generally, however, it can be understood to mean a measurable medical or statistical benefit to a patient or subgroup, respectively, in a given situation.

Executive Summary

that report.[12] Considered a living document, the Roadmap will be refined and expanded as needed to reflect present and future women's health regulatory questions, needs, and priorities.

To foster transparency within and outside FDA, OWH will post the Roadmap on its Women's Health Research website,[13] where information about OWH, including research initiatives, is available. FDA's OWH will launch the Roadmap for use beginning with the fiscal year 2017 grants cycle.

12 FDA's report *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products* is available on FDA's web page at *http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf*. Accessed June 29, 2015. FDA's *Action Plan* to Enhance the Collection and Availability of Demographic Subgroup Data responds to a provision in section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 (P.L. 112-144, July 9, 2012). See priority 1 in FDA's *Action Plan*, available on FDA's website at *http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM410474.pdf*.

13 See the OWH website at *http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/default.htm*. Assessed June 29, 2015.

Executive Summary

OWH has identified the following seven broad goals, areas where additional or new research around FDA-regulated products that are used by women would be beneficial to women's health.

1. **Advance Safety and Efficacy**

   Advance the safety and efficacy and reduce the toxicity of FDA-regulated products used by women

2. **Improve Clinical Study Design and Analyses**

   Improve clinical study design and conduct to better identify and evaluate possible sex differences related to FDA-regulated products

3. **Novel Modeling and Simulation Approaches**

   Evaluate and promote the adoption of novel modeling and simulation approaches that can aid in regulatory evaluation of FDA-regulated products

4. **Advances in Biomarker Science**

   Develop tools and methods that can help identify, evaluate, and qualify predictive or prognostic clinical and non-clinical biomarkers and surrogate endpoints

5. **Expand Data Sources and Analysis**

   Identify, develop, and evaluate data sources and efficient techniques for data mining, data linkage, and large data set analysis that can be used to assess the postmarket toxicity or the safety and effectiveness of FDA-regulated products

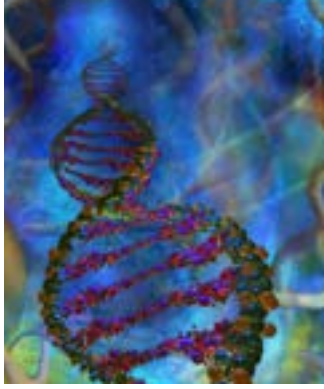
6. **Improve Health Communications**

   Develop, evaluate, and use tools and methods to foster the creation and easy availability of clear and useful information about FDA-regulated products used by women to help women and their health care professionals make informed health-related decisions

7. **Emerging Technologies**

   Support the identification of sex differences related to the use of emerging technologies

Introduction and Background



FDA's Role and Responsibilities

The U.S. Food and Drug Administration (FDA) is a science-based, regulatory agency with the core mission[14] of protecting the public health. FDA plays a significant role in the lives of most Americans. FDA-regulated products touch the lives of most Americans every day. In fact, estimates are that FDA-regulated products account for at least 25 cents of every dollar spent by American consumers each year.[15]

FDA Mission Statement

FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.

FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

Regulatory science, the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products,[16] underpins every regulatory decision FDA makes. The research under way at FDA helps FDA scientists assess the toxicity or the safety, efficacy, quality, and performance of the medical and other products FDA regulates. This research also contributes to advances in science and technology in general and promotes innovation in medical product development and food and cosmetic safety. FDA's research also helps alert the Agency to potential safety issues, like product contamination and other problems that may become apparent only

14 See *http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/budgetreports/ucm298331.pdf*. Accessed June, 2015.

15 See Executive Summary of FDA's *Strategic Plan for Advancing Regulatory Science*, accessed August 2015. Available at *http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm268095.htm*.

16 The entire *Strategic Plan for Advancing Regulatory Science* is available at *http://www.fda.gov/scienceresearch/specialtopics/regulatoryscience/ucm267719.htm*. Accessed June 2015.

Introduction and Background

after a product enters the marketplace.

FDA has a long history of expanding its understanding of the possible different effects of the products it regulates on men and women. The analysis of such possible differences is a routine part of FDA's product review process. For example, FDA has long expected medical product developers to include animals[17] of both sexes when performing preclinical studies of candidate drugs or biological products. Developers must document study results, including on age, sex, the source of the animals being used, and the immediate source of any cell lines and their origins. FDA recommendations vary depending on product area. For example, in nonclinical studies (i.e., not in humans) of medical devices, the difference between species often has a greater influence than the difference between sexes.

It is also important to look for sex differences during clinical testing (i.e., in humans). FDA regulations[18] require the presentation in marketing applications of demographic data (e.g., on age, sex and race) to help identify important information about possible differences among demographic subgroups in the safety or effectiveness of drugs. Developers must analyze safety and effectiveness data, including pooled data for any clinically relevant and statistically significant sex differences, for these demographic subgroups and must include the information in their new drug or biologic applications. FDA has also issued guidance to industry describing how to plan for and analyze clinical data to identify sex-related differences for medical devices.[19] During FDA review of a marketing application, FDA carefully determines whether the available clinical data can be generalized and applied to subgroups. FDA may require additional studies to address areas of concern identified in pre- or postmarket clinical data.

17 Note that FDA is committed to reducing the number of animals used in testing, or eliminating their use all together to the extent possible. One tool that is helping achieve that goal is computer simulation modeling.

18 See 21 Code of Federal Regulations 314.50.

19 See, for example, FDA guidance *Evaluation of Sex-Specific Data in Medical Device Clinical Studies*, available at *http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM283707.pdf*. Accessed August 2015.

Introduction and Background

FDA's Office of Women's Health Research Program

FDA's Office of Women's Health (OWH) was established in 1994 to provide leadership on women's health issues within FDA. OWH's stated mission is to help protect and advance the health of women through policy, science, and outreach; advocate for inclusion of women in clinical trials and analysis of sex effect; and increase scientific knowledge through advanced professional training/education in subpopulation analysis.[20]

In 1994, OWH established a research and development program to undertake the following:

- Advance the evaluation of sex-based differences in the safety and efficacy of FDA-regulated products
- Conduct research on health conditions and diseases that solely or disproportionately affect women
- Track the participation of women and special populations in clinical studies and improve demographic subset analyses
- Advance scientific knowledge through advanced professional training and education in subpopulation analysis and women's health

As of 2015, OWH had funded 340 research projects totaling approximately $35 million. OWH-funded projects, which are typically carried out by FDA centers, have addressed health issues affecting women across their lifespan. Projects have ranged from investigating listeria in pregnancy and cosmetic safety to the study of, sexually transmitted infections, cardiovascular disease, breast cancer, reproductive health, endocrine and neurological disorders, and psychiatric disorders, among other conditions.[21] This research has contributed to safety labeling changes for medical products, new guidance for industry on product development, data standardization for vaccine clinical data, standards for

20 For more information on the OWH, see the website at *http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofWomensHealth/default.htm*. Accessed March 2015.

21 The extent of OWH funding of initiatives related to tobacco products is limited, to some extent, by authorities laid out in statutory language authorizing the Center for Tobacco Products (CTP). CTP funds research related to its statutory authority. Information on CTP research activities, including funding underway and funding opportunities, is available on the CTP website: *http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/AbouttheCenterforTobaccoProducts/ucm292048.htm*. Accessed September 2015.

Introduction and Background

evaluation of tampons and condoms, and evidence-based support for consumer decision about products recommended for use by pregnant women (e.g., the risks and benefits of fish consumption).[22] OWH-funded research has also served as the foundation for the development and expansion of other women's health research activities, including, for example, the National Center for Toxicological Research's annual Women's Health Research Program.[23]

OWH supports FDA's public health and consumer protection mission using multiple approaches. OWH may also lead or coordinate research, policy development, and educational and communication initiatives addressing women's health when they involve multiple FDA centers and/or external collaborators. As described in the box below in more detail, the Office of Women's Health Research Program supports a variety of activities, including, for example, intramural research grants, FDA research program collaborations, external research collaborations, workshops and training, and OWH conducted research. As described in the box below in more detail, the Office of Women's Health Research Program supports a variety of activities, including, for example, intramural research grants, FDA research program collaborations, external research collaborations, workshops and training, and OWH conducted research.

The OWH Research and Development Program plays an integral role in promoting sound policies and regulations by supporting research projects, workshops, and training to help FDA answer regulatory questions related to women's health.

22 Obias-Manno D, Scott PE, Kaczmarczyk J, et al. The Food and Drug Administration, Office of Women's Health: Impact of Science on Regulatory Policy. J Womens Health 2007 July-Aug; 16(6)807-17, available at *http://www.ncbi.nlm.nih.gov/pubmed/17678451*. Accessed March 2015. *Note: a second article is in development describing more recent contributions of OWH-funded research.*

23 This event is a result of OWH funding. NCTR scientists and other experts present scientific findings on women's health.

Introduction and Background

Office of Women's Health Research Program

Intramural Research Grants

- **Competitive Grants**: Peer-reviewed grants are awarded to FDA-scientists who respond to an annual call for proposals from OWH.
- **Special Funding Initiatives**: Special projects are awarded to FDA scientists outside of the competitive process to respond to emerging and pressing women's health issues. These funds can also be used to support workshops, surveys, and focus group testing.

FDA Research Program Collaborations

- FDA product centers and offices directly support scientific research in the form of grants, cooperative agreements, or contracts. OWH collaborates with other FDA research programs, like the Critical Path Initiative* to better integrate women's health research questions into their research activities.

External Research Collaborations

- These may involve special projects conducted with other governmental agencies and other external partners to help FDA leverage all available technologies, expertise, and resources when addressing complex research questions.

OWH Workshops and Training

- Scientific workshops and trainings/curriculum development for health professionals are designed to advance the understanding of women's health and sex-related differences.

OWH Conducted Research

- OWH projects have been launched to assess the level of participation by women and analysis of outcomes by sex in clinical trials in support of product applications submitted to FDA.

* *For more on the Critical Path Initiative, see FDA's webpage at http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/default.htm. Accessed November 2015.*

The Importance of Women's Health Research

Women's health research is critically important. We know that disease sometimes manifests differently in women than in men; sometimes women also respond differently to FDA-regulated products. A number of factors can influence these differences. Intrinsic factors (e.g., genetics, hormones, body size, sex-specific physiology), extrinsic factors (e.g., diet, sociocultural issues, environment),

phenotypic differences,[24] or interactions among these factors can play an important role in how women respond to therapies. Characteristics associated with female sex (e.g., size, age, co-morbidities, past pregnancies) may be associated with differences in the safety or effectiveness of a particular medical product.

Because these differences in health, disease, and treatment response can occur throughout a woman's life span—and may be substantial, depending on her stage of life—a deeper analysis is needed of how regulated products work in diverse populations of women. For example, fluctuations of hormones across the lifespan can affect clinical outcomes: the loss of estrogen due to oophorectomy; menopause, whether natural or premature, contributes to loss of bone mineral density, which can lead to osteoporosis, increased risk of fracture, and increased morbidity and mortality. Thus, it is important to understand whether and how hormonal changes affect product performance at the onset of puberty, during the menstrual cycle, during pregnancy, and during the transition from pre-menopause, to peri-menopause, to post-menopause. We must improve our understanding of how to identify and interpret sex differences in addition to understanding how these differences might affect treatment. This is especially important, given the many evolving new technologies and scientific fields, such as nanotechnology; pharmacogenomics; stem cells; advanced manufacturing techniques, like 3-D printing[25]; and novel imaging techniques and methods used to improve diagnosis. Advances in our understanding in these areas will contribute to FDA's ability to carefully evaluate the many innovative therapeutic products in the development pipeline.

New clinical trial and study designs, such as adaptive and enrichment studies, could help ensure effective use of small samples and sub-population analyses. New methods, processes, and tools, including modeling (e.g., in vitro and computational modeling) and other novel technologies, can help evaluate medical device designs, predict toxicity, or predict the safety and efficacy of FDA-regulated products and guide medication dosing for women. Biomarkers, surrogate

24 Phenotypic differences are the observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences.

25 3-D manufacturing/ 3-D *printing* also known as *additive manufacturing* involves building an object by *printing* something layer by layer.

endpoints,[26] patient reported outcomes,[27] and other tools are increasingly being used during medical product development and in the clinic to help understand disease, therapy, and patient response to therapy. Advances in the science of biomarkers could help improve our understanding of the molecular underpinnings of disease in women and provide the data necessary to evaluate the safety and effectiveness of medical products, leading to advances in personalized, or precision, medicine.[28]

It is also critical to gain a better understanding of how to incorporate and interpret data, including data from clinical trials carried out in other countries, which may not be consistent with U.S. demographic profiles, during premarket review and during surveillance once therapies are on the market and being used by women.

Last but not least, the information gained from this research must be clear and readily available to multiple diverse subpopulations of women to help them and their health care professionals make informed choices about the regulated products available to them. Social science research can help identify and evaluate methods for eliciting patient perspectives on disease, treatment options, and effects of treatment and for delivering information to women and determining how

26 Section 4 of this report discusses *biomarkers* in more detail. Generally speaking, a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Strimbu K and Tavel JA. 2010. What are *biomarkers*? *Curr Opin HIV AIDS* 2010; 5: pp. 463–466). *A surrogate endpoint* is a biomarker that predicts the clinical benefit (or harm, or lack of benefit) of a treatment based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence (Feigin A. 2004. Evidence from *Biomarkers* and Surrogate Endpoints. NeuroRX 2004: 1 (3): pp. 323-330). A clinical endpoint is a characteristic or variable that reflects how a patient feels, functions, or survives (Sullivan EJ. Clinical Trial Endpoints). Available at: *http://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM283378.pdf*. Accessed March 2015.

27 A *patient reported outcome* (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on a symptom or group of symptoms, on effects on a particular function or group of functions, or on a group of symptoms or functions shown to measure the severity of a health condition. PRO instruments have proved useful in assessing medical product labeling claims. See, for example, FDA guidance, available at *http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf*. Accessed June 2015.

28 Also known as *individualized treatment*, or *targeted therapy*, precision medicine makes use of blood tests, images of the body, or other technologies to measure individual factors called *biomarkers*. These *biomarkers* can then be used to determine who is most likely to benefit from a treatment, who is at higher risk of a side effect, or who needs a different dose. For more, see *http://blogs.fda.gov/fdavoice/index.php/2015/03/fda-continues-to-lead-in-precision-medicine/*. Accessed September 2015.

Introduction and Background

individual factors like sex, age, culture, and health literacy might affect consumer understanding of product labeling and other FDA communications about regulated products.

FDA is interested in any patient or population characteristics that might affect the course of a disease or condition or the toxicity, safety, or effectiveness of an FDA-regulated product available to women. The goal is not just to identify that differences exist from one subpopulation to the next. The goal is to determine when identified differences have clinically meaningful[29] effects on patient health. This information can then be used to guide clinical decisions about the optimum course of action and inform the development of better diagnostic and therapeutic products for all subpopulations of women.

By promoting collaborative research in mission critical areas, developing new tools, applying this new knowledge during FDA's review process, and strategically coordinating the findings so that they inform regulatory and policy decisions, FDA will be better positioned to foster the advancement of innovative products that promote and protect the health of all Americans.

Developing the Roadmap

In 2013, OWH launched a process to develop a new research strategy, a roadmap that could build on knowledge gained from previously funded research and assist OWH in coordinating future health research activities with other FDA research programs and with external partners. As part of the process of developing the Roadmap, OWH evaluated its existing research portfolio to determine regulatory impact. OWH performed a gap analysis to identify critical women's health issues that have not been addressed and conducted discussions with representatives from FDA's centers and offices to identify additional women's health research priorities and related policy questions. Based on information gained through this process, OWH developed a list of proposed research areas considered to be high priority. The list was then vetted within FDA. Because we view the Roadmap as a living document, we will revise it over time, as needed.

29 The definition of *clinically meaningful* can vary depending on the disease or condition being considered, the therapy under consideration, and the goal of therapy. Generally, however, it can be understood to mean a measurable medical or statistical benefit to a patient or subgroup, respectively, in a given situation.

Introduction and Background

While identifying these priority research areas, OWH decided to focus on areas where advancements around FDA-regulated products used by women would be directly relevant to FDA as it makes regulatory decisions related to the toxicity or the safety, efficacy, and security of FDA-regulated products in women.[30] Future research projects supported by OWH through the Roadmap must align with FDA's priorities and strategic goals[31] and with the expectations laid out in the Roadmap. Projects should focus on gaps in knowledge about FDA-regulated products used by women and directly inform FDA's scientific and regulatory decisions related to these products.

OWH's goal in developing the Roadmap was to provide a science-based framework within which to build women's health science into all of FDA's research activities. Using the Roadmap, OWH can make funding decisions that are aligned with FDA's research priorities. The Roadmap will ensure the efficient use of FDA resources while addressing the women's health research questions that are especially important to FDA's regulatory decision making. The Roadmap will also serve as a catalyst for future collaborations intended to help protect and promote the health of women through advancements in policy and science and through outreach. The Roadmap is considered such an important component in FDA's current activities related to optimizing women's health that it was designated a key FDA commitment in FDA's August 2014 *Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data*.[32]

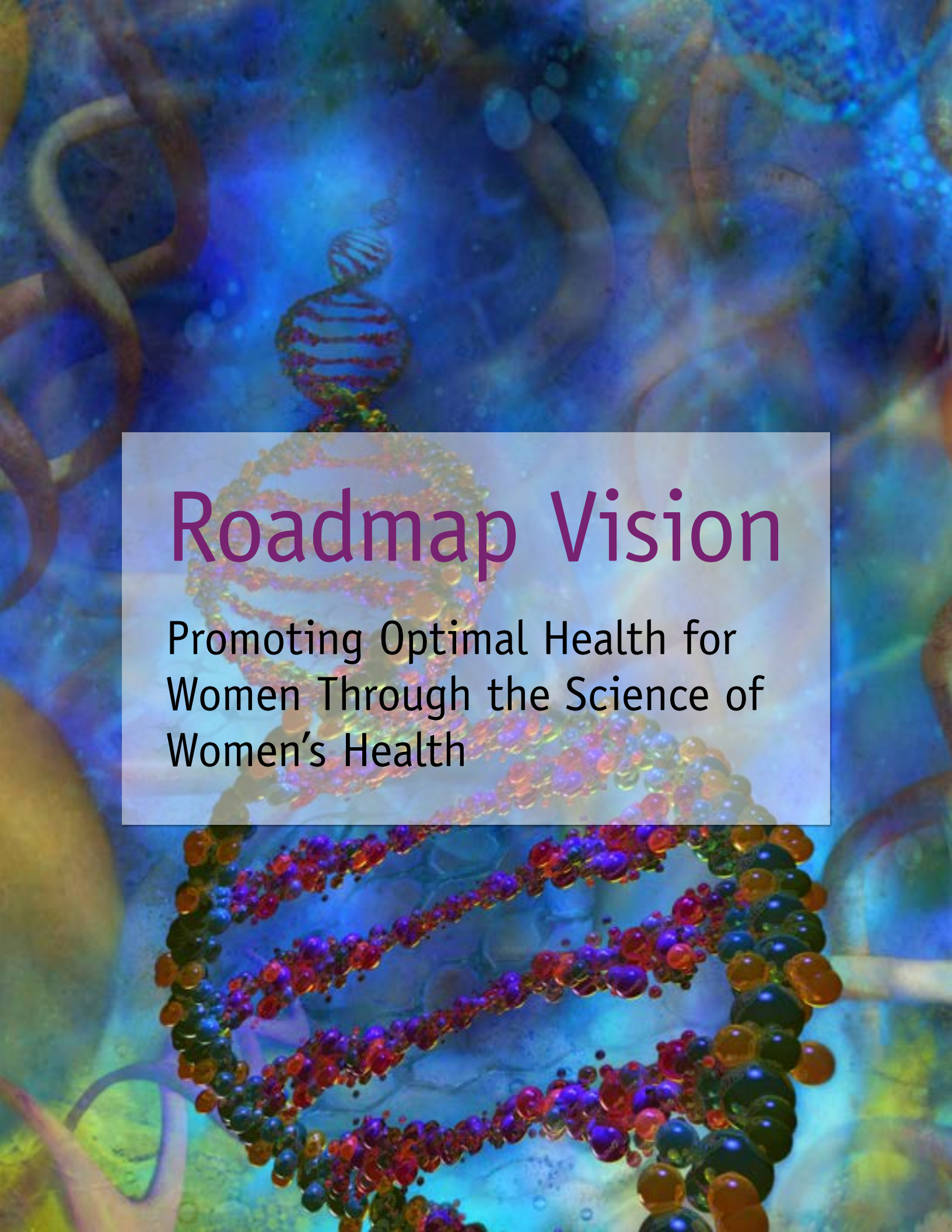
Definition of Woman

It is important to note that although there are differences among FDA centers on the definition of adult, for the purposes of the research that will be supported through the Roadmap, we generally define an adult as an individual 17 years or older. Additionally, FDA acknowledges the complex and evolving research needs related to transgender populations. OWH intends to include transgender-related research as it relates to FDA regulatory products.

30 Many important women's health issues exist that are not directly related to regulatory decision making. To address these issues, OWH is committed to building collaborations or lending technical expertise in capacities other than direct OWH funding.

31 For example, FDA issued its *Strategic Plan for Advancing Regulatory Science*, available at *http://www.fda.gov/scienceresearch/specialtopics/regulatoryscience/ucm267719.htm*. Accessed June 2015.

32 The 2014 *Action Plan* is available on the FDA webpage at *http://www.fda.gov/downloads/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm410474.pdf*. Accessed September 2015. The *Action Plan* was provided for in Section 907 of the Food and Drug Administration Safety and Innovation Act (FDASIA).



Roadmap Vision

Promoting Optimal Health for Women Through the Science of Women's Health

The Research Roadmap

The Office of Women's Health used a three-pronged strategy to develop the areas of focus for the Roadmap. We evaluated our existing research portfolio to determine regulatory impact and performed a gap analysis to identify critical women's health issues that have not been addressed. We also consulted with internal and external stakeholders from the scientific community to identify women's health research priorities and regulatory questions. We then developed a list of research priorities and questions that was vetted with key stakeholders within FDA. The following seven research areas were identified as areas where new or enhanced research is essential to OWH's and FDA's mission.

1. **Advance Safety and Efficacy**
2. **Improve Clinical Study Design and Analyses**
3. **Novel Modeling and Simulation Approaches**
4. **Advances in Biomarker Science**
5. **Expand Data Sources and Analysis**
6. **Improve Health Communications**
7. **Emerging Technologies**

In the following sections, we discuss each of these research priority areas in more detail, emphasizing areas of possible focus, noting how the research could support FDA activities, and highlighting how the research can advance public health. A few examples of specific research objectives are also provided.

1 Advance Safety and Efficacy

Advance the safety and efficacy and reduce the toxicity of FDA-regulated products used by women.

Proposed research in this priority area should take a comprehensive look at the diseases and conditions primarily affecting women and the areas where additional research is needed to advance our understanding of disease and treatment in women in particular. It should focus on health areas of unmet medical need and scientific gaps related to FDA-regulated products, such as those outlined in the IOM report[33] on knowledge gaps in women's health. Research should explore how sex differences may affect medical product safety and effectiveness or play a role in the use of other regulated products (e.g., cosmetics). Research should also explore the possible effects on diverse and special subpopulations of women across the lifespan (e.g., reproductive age women, pregnant women, post-menopausal women, elderly women).

FDA will use the results of this research to advance the understanding of disease presentation and manifestation in women, the mechanisms of action of regulated products, and women's response to therapies to treat those diseases. This research should expand FDA's capacity to effectively evaluate FDA-regulated products used by women throughout all life and disease stages.

Potential health impacts of this research include gaining a better understanding of diseases in specific subpopulations of women (e.g., elderly women,[34] pregnant women), which should enhance the ability of patients and their health care professionals to make appropriate treatment decisions. Advances in the science of women's health, especially in areas of unmet medical need or in diseases or conditions with a large public health burden, will advance women's health in general.

33 See Institute of Medicine. 2010. *Women's Health Research*: *Progress, Pitfalls, and Promise*. Washington D.C.: The National Academies Press.

34 Generally, considered to be persons who are 65 years old and older.

Advance Safety and Efficacy

Objectives

1.1 Advance our understanding about diseases and conditions that primarily affect women, such as breast health, reproductive issues, obstetric and gynecological issues, and biocompatibility issues related to implants used in women

1.2 Expand evaluation of regulated products for disease areas where additional research is needed to advance our understanding of disease prevention, presentation, manifestation, and treatment in women that may be different from those in men; promote innovation in product development; or address disparities affecting women, to include, but not limited to major causes of mortality and morbidity such as:

- Autoimmune disease
- Cancer
- Cardiovascular disease
- Diabetes
- HIV/AIDS
- Lung Disease
- Neurological conditions
- Osteopenia/Osteoporosis
- Psychiatric disorders

1.3 Improve our understanding of the apparent role of sex-correlated co-morbidities, concomitant medications, other subgroup differences (e.g., age, race, obesity, body size, physiology) and metabolism of drugs and biologics on the toxicity or the safety and efficacy of FDA-regulated products

1.4 Evaluate the role of sex hormones on the efficacy and safety of medical products

Advance Safety and Efficacy

1.5 Develop tools and methods in support of development of diagnostics and therapeutics targeting specific subpopulations of women, including, but not limited to:

- Develop tools and methods to evaluate innovative, new devices and diagnostics specifically designed for use in women (e.g., gynecological devices)
- Develop tools and methods to enhance the evaluation of devices used in both men and women to take into consideration sex differences like organ size/anatomy/physiology/human factors differences that may affect device performance
- Foster development of tools and methods to evaluate *sex-matched*[35] devices and companion diagnostics

1.6 Enhance our understanding of how FDA-regulated products work in sub-populations of women, including, but not limited to the following examples:

- Elderly Women – Identify sex-specific biomarkers for disease progression and treatment outcome in elderly women, including elderly women with comorbid conditions and those who take multiple therapeutic agents
- Pregnant Women – Enhance our understanding of the toxicity or the safety and effectiveness of FDA-regulated products used during pregnancy
- Lactating Women – Evaluate the safety of drugs, biologics, and potential toxicants, including from tobacco or tobacco smoke, and materials used in manufacturing medical devices, that may be transferred into breast milk and to nursing infants
- Pre- and post-menopausal Women – Investigate how the effects of hormonal changes and reproductive transition in pre- and post-menopausal women may affect the toxicity or the safety and efficacy of FDA-regulated products

35 *Sex-matched devices* are devices that are typically used in both sexes, but for which there are specific versions with specific claims for women. An example is a set of orthopedic implants that have specific sizes and shapes intended for women.

2 Improve Clinical Study Design and Analyses

Improve clinical study design and conduct to better identify and evaluate possible sex differences related to FDA-regulated products.

Research in this area should help develop and promote use of better methodologies for identifying and evaluating sex differences and best practices for recruitment and retention of women. The identification of sex differences in clinical study data should help determine areas needing further exploration. For example, we need a better understanding of the biological basis of sex differences and how differences can affect the toxicity or the safety and efficacy of FDA-regulated products. Improvements to clinical study designs to facilitate identification of sex differences will complement other efforts to break down any remaining barriers to including women in clinical trials and increase the recruitment and retention of diverse populations of women in trials.

Collecting sufficient, high-quality data on women during clinical studies will help enable better analyses for identifying disparities.

Objectives

2.1 Develop and promote use of clinical study designs (e.g., adaptive designs, observational studies, registries) and statistical methods (Bayesian methods, meta-analyses) to evaluate sex differences and perform other subset analyses with regard to the toxicity or the safety and efficacy (or effectiveness) of FDA-regulated products, including, but not limited to the following:

- Determine how to properly incorporate and interpret data generated in clinical trials conducted in other countries specific to women or sex differences that may not be consistent with U.S. demographic profiles, especially when U.S. data are not available or are incomplete
- Develop methods for adaptive and enrichment studies to support the effective use of small sample sizes in clinical trials and studies

Improve Clinical Study Design and Analyses

- Develop analytical methods for interpreting and using data on sex differences from trials and studies with small sample sizes
- Determine how best to incorporate electronic health records with other trial data when evaluating pragmatic clinical trials[36]

2.2 Identify and evaluate best practices for the recruitment and retention of women in clinical trials (e.g., new strategies, approaches)

2.3 Identify appropriate endpoints and outcome measures, including patient-reported outcome measures, for diseases or medical products that may affect women differently from men (e.g., certain types of cardiovascular disease present differently in men than in women)

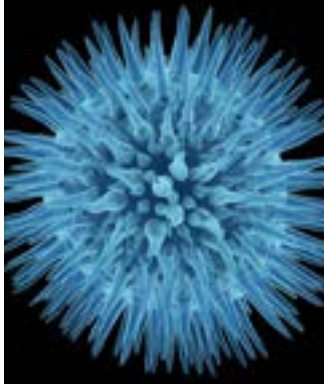
2.4 Determine how best to define the *appropriate* representation of women in a given trial or study:

- Identify standards such as background information needed to develop metrics
- Develop and evaluate metrics to measure the level of representation of demographic subgroups in clinical trials supporting FDA-regulated product approvals and marketing authorizations
- Evaluate to what extent the definition of the appropriate representation will affect the ability to identify sex differences (i.e., does your metric result in a sufficient number of women being included to reveal possible sex differences?)

2.5 Develop approaches and tools to track the inclusion of women in clinical trials, their demographic profiles, and the extent of subset analysis

36 *Pragmatic* trials or studies refer to trials or studies carried out as part of routine clinical practice, rather than as trials or studies performed under strictly controlled conditions.

3 Novel Modeling and Simulation Approaches



Evaluate and promote the adoption of novel modeling and simulation tools and approaches that can aid in regulatory evaluation of FDA-regulated products

New animal and computer simulation modeling techniques[37] are creating innovative opportunities to identify and evaluate sex differences. These techniques can be used to facilitate the study of products at the level of the mechanism of action. These techniques can also be used to predict the toxicity or the safety and efficacy of FDA-regulated products in women including in certain sub-populations (e.g., pregnant women) as well as guide therapy selection and medication dosing for women.

Research in this area should help create predictive models that can take into consideration sex, disease status, and comorbidities, among other critical factors, that may influence the performance of an FDA-regulated product. Research should also help develop models that incorporate sex-specific biomarkers (see next section) that can advance our understanding of unique ways women experience disease manifestation and response to treatment. Better predictive preclinical data from improved models is especially relevant for women as they are more susceptible to some adverse events.[38]

Research in this area holds the promise of yielding results with major public health benefits. For example, better *in silico* modeling and simulation of clinical trials (i.e., using computers) hold the promise of strengthening the ability to predict efficacy and adverse events during clinical trials while reducing sample size,

37 FDA is committed to reducing the number of animals used in testing or eliminating their use all together to the extent possible. Computer simulation modeling is one tool that is helping achieve that goal.

38 For example, *Torsades de Pointes* is a potentially fatal arrhythmia associated with longer QT interval in the ECG. Women are more prone than men to develop *torsades de pointes* with certain drugs (70% of drug-induced Torsades cases occur in women). See Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. 1993. *JAMA*. Dec 1;270(21):2590-7; and Ebert SN1, Liu XK, Woosley RL. 1998. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. *J Womens Health*. 1998. Jun;7(5):547-57.

Novel Modeling and Simulation Approaches

making trials more efficient and potentially safer for trial participants. These new techniques can help improve the efficiency of nonclinical and clinical studies, helping to identify promising candidate products earlier in the medical product discovery and development process. This means that safe, new medical products may reach the patients who need them sooner. These new tools can also help identify and characterize contaminants in foods and supplements and predict related outcomes.

Objectives

3.1 Develop new and leverage existing tools and novel animal, in vitro, and computational models, including those for use in clinical trials to study the toxicity or the safety and efficacy of FDA-regulated products used by women and to study sex differences. Examples include, but are not limited to the following:

- Develop in vivo, in vitro, and computational models to evaluate regulated-product toxicity or the safety and efficacy during pregnancy
- Foster the development of innovative disease models for conditions that affect women, including for rare diseases
- Foster the continued development of models that incorporate human genetics, genomics, molecular signatures, and biomarkers for diseases influenced by sex
- Determine factors relevant to therapy selection and medication dosing considerations in women
- Dietary supplements and toxicity differences
- Identify unique risks that arise for women in the use of specific regulated products to further evaluate the effects of factors that are of concern for female users. For example, products aimed at weight-loss, or mood-alteration, have a large user base of women, and sex or gender-associated risks need to be clearly identified and considered for such products.
- Identify categories of products that would be expected to have differential risk profiles for women vs men; develop a framework as to how the differential risk should be captured and weighed in assessing the toxicity or the safety and effectiveness evaluation of the product. For example, one unique consideration that may arise for female consumers is contact exposure through use of gender-specific topical products such as transdermal estrogen that may result in inadvertent product transfer to others. Because women tend to associate more with children as care-givers, such differential factors should be explicitly identified and evaluated for specific products.

4 Advances in Biomarker Science

Develop tools and methods that can help identify, evaluate, and qualify predictive or prognostic clinical and non-clinical biomarkers and surrogate endpoints

A *biomarker* is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or biological responses to therapeutic intervention. A biomarker can be a physiologic, pathologic, or anatomic characteristic or measurement that is thought to relate to some aspect of normal or abnormal biological function or process.[39] Research in this area is expanding rapidly. Nevertheless, more research is needed to identify biomarkers for assessing medical product safety and efficacy in women throughout a product's life cycle, including facilitating predictions in preclinical development that can be used during product development as well as in monitoring safety after marketing (e.g., during postapproval testing and surveillance).

A biomarker can be used as a *surrogate endpoint*, that is, as a substitute for a clinical endpoint. A surrogate endpoint would be expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. Surrogate endpoints are a subset of biomarkers and have been used to establish therapeutic efficacy in pivotal studies or confirmatory studies used to grant accelerated marketing approval for certain therapeutics.

39 There are various types of *biomarkers*. Examples include *diagnostic biomarkers* to identify the presence or absence of a specific physiological or pathophysiological state or disease; *prognostic biomarkers* to help identify and categorize patients by degree of risk for disease occurrence or progression or to inform about the natural history of a disorder in a particular patient in the absence of a therapeutic intervention; and *predictive biomarkers* to help identify and categorize patients by their likelihood of response to a particular treatment and to help identify a subpopulation likely to respond to a treatment intervention in a particular way. For more on *biomarkers*, see FDA *Guidance for Industry and FDA Staff, Qualification Process for Drug Development Tools*, available on FDA website at *http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf*. Accessed May 2015. See also *Biomarkers* Definitions Working Group (2001). *Clinical Pharmacology and Therapeutics*, 69, p. 89–95, available at *http://onlinelibrary.wiley.com/doi/10.1067/mcp.2001.113989/abstract*. Accessed July 2015.

Advances in Biomarker Science

Biomarkers can be used to help ensure that safety issues specific to women can be identified early in medical product development and that women enrolled in clinical trials can avoid ineffective or unsafe treatments. Additionally, biomarkers may be able to identify differences in response to an FDA-regulated product resulting from other factors, like age, sex, and ethnicity, and drug interactions.

Research in this area should help FDA identify and qualify biomarkers that can better measure and predict toxicity or the safety and efficacy of FDA-regulated products in women in non- or preclinical studies and during clinical trials. Important considerations in biomarker development include, for example, pre-analytical considerations such as sample collection, storage, and transport to ensure analyte/sample stability; the use of analytically validated (i.e., with adequate sensitivity, specificity, accuracy, reproducibility) assays to ensure reliable biomarker data; and reproducibility using a *learn and confirm* paradigm (i.e., use of datasets to test and confirm). For biomarker qualification, additional considerations include context of use (COU) of the biomarker in drug development; biological rationale for use of the biomarker; and characterization of the relationships among the biomarker, the clinical outcomes, and the treatment (where applicable) required for the proposed COU.

Public health in general will benefit from research in this area. For example, sex-specific biomarkers could be used to identify how men and women respond differently to medical products, improving the availability of safe and effective medical products for all Americans. More specific biomarkers could also help increase the efficiency of clinical trials and accelerate the movement of beneficial medical products to the market.

Objectives

4.1 Identify, develop, and evaluate biomarkers to be used in the assessment of products related to conditions that affect women and in the identification of sex differences in the performance of medical products for other conditions:

- Assess the sensitivity, specificity, accuracy, reproducibility of biomarkers
- Document the evidence supporting the correlation of identified biomarkers as indicators of health or disease processes, or therapeutic response

5 Expand Data Sources and Analysis

Identify, develop, and evaluate data sources and efficient techniques for data mining, data linkage, and large data set analysis that can be used to assess the postmarket toxicity or the safety and effectiveness of FDA-regulated products

Clinical trials for product approval or marketing authorization are conducted in controlled settings. As a result, they cannot uncover or predict all adverse events that might occur during broader clinical use. Some toxicity and safety issues are revealed only after a product is marketed and used in a larger, more diverse population under uncontrolled, variable clinical conditions (real world). FDA is committed not only to support research that facilitates the premarket review of medical products, but also to fund research on marketed products to assist in assessing whether these products are promoting and protecting public health for the diverse subpopulations of women who are using them.

Relevant research OWH has supported in the past includes improving safety signal[40] detection, data mining capabilities, and data standardization to enable the use of postmarket data to evaluate the toxicity or the safety and effectiveness of FDA-regulated products. Identifying and using various postmarket data sources is especially critical for gathering informative evidence for special populations of women like pregnant or post-menopausal women using regulated products.

Advances in this area promise numerous benefits. The capability to integrate and interpret diverse data should enable FDA to use its considerable repositories of data from product submissions and adverse event reports more efficiently, in

40 The phrase *safety signal* refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. *Safety signals* can arise from postmarket data, preclinical data, and events associated with other products in the same pharmacologic class. For more, see FDA guidance *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*. Available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf. Accessed March 2015.

Expand Data Sources and Analysis

combination with data from electronic medical records, claims data, registries, and basic science research to identify potential efficacy and safety or toxicity issues for women related to the use of regulated products. Research in this area should give FDA additional tools to help identify adverse events in women and predict and minimize adverse events through regulatory actions, such as labeling changes or considerations of product withdrawal from the market. A real benefit would be the identification of data that are useful to support label expansions or changes in practice patterns when groups of patients outside the initial labeled indication are identified for whom benefits outweigh risks.

The potential public health benefits of advancements in evaluating the toxicity or the safety, effectiveness, and security of FDA-regulated products in the postmarket setting are substantial. Advances should provide the scientific data and the tools needed to strengthen existing surveillance networks and help identify and understand possible security, safety, and toxicity issues of importance for the diverse subpopulations of women and for all demographic groups. These strategies will continue to be translated into tools that improve surveillance for all Americans.

Objectives

5.1 Evaluate and validate U.S. and international postapproval or postmarket data sources for use in the identification of the potential effects of sex differences on the toxicity or the safety, effectiveness, and security of FDA-regulated products used by women:

- Registries
- Electronic health records
- Surveillance databases
- Clinical outcomes data
- Medicare and other claims data
- Information gathered in pragmatic trials
- Adverse event reports

Expand Data Sources and Analysis

5.2 Evaluate methodologies for the identification of clinically relevant sex differences, using a variety of postmarket data sources

5.3 Conduct studies using postapproval or postmarket data sources to evaluate the toxicity or the safety, effectiveness, and health effects of FDA-regulated products used by women, including the examination of sex differences

5.4 Develop efficient data mining and analysis techniques that can be used on data sets that can specifically identify women's health issues on a larger scale. Such techniques have the added value of being beneficial when analyzing premarket as well as postmarket data sources, like clinical data repositories

6 Improve Health Communications

Develop, evaluate, and use tools and methods to foster the creation and easy availability of clear and useful information about FDA-regulated products used by women to help women and their health care professionals make informed health-related decisions.

One of FDA's strategic priorities[41] is to provide consumers and health professionals with the information they need to make informed decisions about the use of FDA-regulated products. Research in this area should identify and evaluate methods for communicating FDA information, including product information and risk communications, to diverse subgroups of women. Research should take a comprehensive look at individual and situational factors that may influence the understanding and use of such information. Additionally, specific strategies should be explored for communicating risk–benefit information to any subpopulations who may find product use or risk information unclear (e.g., for limited English proficient speakers). Public health information cannot be useful to consumers if it isn't tailored to the intended audience and easily accessible.

With a better understanding of how to create effective communication strategies to more effectively reach specific subpopulations of women, FDA can provide patients and their caregivers clear and useful health-related information.

Research in this area should help ensure that women receive product risk (e.g., toxicity, safety) and benefit information tailored to their needs. Health care professionals will also benefit from clear and readily available prescribing, dispensing, and product use information.

41 See strategic priority # 8 of FDA's *Strategic Plan for Advancing Regulatory Science*, available at *http://www.fda.gov/scienceresearch/specialtopics/regulatoryscience/ucm267719.htm*. Accessed September 2015.

Improve Health Communications

Objectives

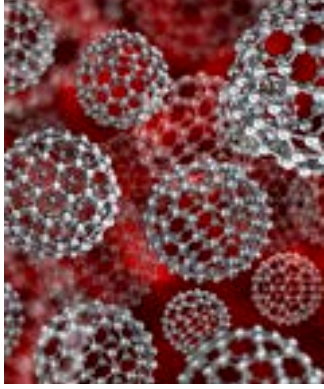
6.1 Identify how factors related to an individual (e.g., sex, gender, age, literacy level, native language) can affect a woman's understanding of FDA product information and its influence on her subsequent health-related decisions

6.2 Evaluate the reach and impact of FDA communications about FDA-regulated products used by women, including but not limited to identifying and evaluating methods for communicating:

- FDA information to special populations of women, including elderly women, women with disabilities, caregivers, pregnant women, and women with limited English proficiency
- Specific information about sex and gender differences
- Risks of certain medical product exposures, food consumption (e.g., seafood), and the use of tobacco products during pregnancy
- Information about drug exposure during breast-feeding

6.3 Explore methods for using social media to identify gaps in knowledge, misinformation, or sentiments about specific women's health issues and related FDA regulated products. Identify and evaluate possible issues related to how social media is being used by others to inform about FDA-regulated products

7 Emerging Technologies



Support the identification of sex differences related to the use of emerging technologies

Science and medical care continue to evolve, and new medical technologies and scientific fields continue to emerge. These include nanotechnology, pharmacogenomics, novel imaging technologies and methods, 3-D printing, and developments in regenerative medicine, to mention but a few. Advances in these areas should be accompanied by development and adoption of new methods and tools for evaluating new technologies in a way that considers sex and gender factors. Moreover, research in this area should enhance FDA's ability to evaluate innovative products and novel technologies, which may help to efficiently integrate beneficial new products into health care for women. FDA must also be able to acquire and use new and emerging technologies to advance its research activities. Although it is beyond the capabilities of OWH to support FDA's acquisition of new technologies and facilities, OWH will support studies to advance the understanding of the possible effects of sex differences on the use of these new technologies and scientific fields.

Public health will benefit from this research as long as we can be sure that novel technologies that have the potential to change the landscape of medicine will benefit women. Additionally, the consideration of sex differences during the development of new technologies will facilitate advances in precision therapy.

Emerging Technologies

Objectives

7.1 Examine sex differences early in the development of innovative health products, new materials, and novel assessment tools and methodologies, including but not limited to the following:

- Nanotechnology
- Precision medicine
- Pharmacogenomics (metabolomics, epigenetics)
- Novel imaging technologies and methods for improved diagnosis
- 3-D Printing
- Stem cells and regenerative medicine and stem cell technology
- *In silico* modeling

Moving Forward

FDA's OWH will launch the Women's Health Research Roadmap beginning with the FY 2017 grants cycle. The conversations, feedback, and analysis during the Roadmap's planning and vetting phases have laid the groundwork for implementation. OWH will undertake the following as it begins to identify, review, and fund research projects in the seven priority areas.

Enhance Intra-Agency Collaboration

OWH will work with FDA centers to increase collaboration and communication across research endeavors related to women's health. This will include increasing alignment of the OWH funding programs to support center research projects.

Establish a Formal Women's Health Research Steering Committee (WHRSC)

Once fully formed, the WHRSC, with representatives from FDA centers and key offices, will help identify and refine research priorities and enhance collaboration and communication within FDA and with external stakeholders. One of the WHRSC key roles will be to assist OWH in staying abreast of advances and emerging issues affecting women's health and scan the horizon for important women's health research areas. The WHRSC will also help expand and refine metrics for assessing program success and align funding decisions with FDA's regulatory science priorities

Implement Mechanisms to Facilitate Women's Health Research

OWH will revise the current OWH grant funding structure and requirements to better support cross-center collaborative projects. For example, OWH will consider projects that exceed the previous funding cap and time limits, provided the scope and impact of the projects merit such consideration, and there is a high degree of cross-center and/or external collaboration. This new funding structure should enable a more comprehensive analysis of the factors affecting toxicity or safety and efficacy. In some cases, OWH will ask for support (e.g., personnel and/or resources) from the centers.

Revisions to the current approach will enable OWH to supplement research underway to incorporate the examination of sex and gender differences.

For example, grants will be awarded for adding animals, tissues, cells, or subjects to original grants to facilitate sex analyses (e.g., adding subjects of the opposite sex to a single sex or gender study; adding more subjects of either sex to a sample of both males and females to increase the statistical power of sex analyses) and for further exploration of the mechanisms of any sex differences observed in previously OWH-funded or other FDA-funded projects.[42]

Improve General Funding Criteria

Based on input from stakeholders while developing the Research Roadmap, OWH identified important factors to consider when identifying research projects for OWH Funding. For example, does the research align with the principles outlined within the Roadmap and with FDA's priorities and strategic goals? Research addressing a knowledge gap in relation to public health needs of women or where women have few therapeutic options would be viewed favorably. Specific research funding guidelines surrounding these factors will be defined by OWH and the WH Steering Committee.

The OWH funding mechanism seeks to increase collaboration across FDA centers. For example, OWH would be very interested in supporting new health research projects in the centers, or projects already underway in the centers, that focus on women's health issues. OWH will also continue partnering with investigators who previously received OWH grants when their research appears to be leading to successful outcomes, or OWH-sponsored work that may require additional support to achieve a successful outcome.

In summary, when selecting projects for funding, OWH will consider a number of factors, for example:

- Does the research address a priority area outlined in the Roadmap?
- Is the research aligned with FDA's regulatory science priorities or other strategic goals?
- Does the project address a regulatory question with the potential for regulatory impact, policy changes, or revised industry standards?

42 This project mirrors a similar effort underway since 2013 at the National Institutes of Health. See News and Events announcement at *http://www.nih.gov/news/health/sep2014/od-23.htm*. Accessed March 2015.

Moving Forward

- Does the project address an area of unmet public health or an area where women have few therapeutic options?

OWH will also consider whether the project is an outgrowth or extension of research previously funded by OWH that has demonstrated the potential to produce regulatory impact or significant scientific impact and if the research addresses issues that can be investigated through collaborations across the FDA centers. Research funding priorities will be refined as needed by OWH and the Women's Health Research Steering Committee.

Conclusion

Over the past decades, substantial progress has been made to better understand the factors affecting the toxicity or the safety, efficacy (or effectiveness), and security of FDA-regulated products used by women. Since its establishment in 1994, OWH has funded numerous research projects that have expanded our understanding of the science of women's health and aided FDA as it makes important regulatory decisions.

The goal of this Roadmap is to continue that progress by creating a formal framework for OWH funding decisions beginning with the 2017 funding cycle. The Roadmap champions women's health science and is intended to ensure the efficient use of FDA resources while addressing the women's health research questions that are especially important to FDA's regulatory decision making and communications efforts. The Roadmap is another key step confirming OWH's critical role in ensuring that FDA continues its science-based, priority-focused approach to addressing the complex and rapidly changing regulatory challenges related to women's health. The Roadmap's development has already served as a catalyst for better collaboration, new and potential partnerships, internal alignment, and public transparency.

Because it is considered a living document, we intend to refine and expand the Roadmap as needed to reflect present and future women's health regulatory questions, needs, and priorities. We believe that successful implementation of the Roadmap, including through partnerships with other governmental agencies, industry, and academia, will better position FDA to answer key regulatory questions about new technologies and fulfill its regulatory mission to protect and promote public health. The Roadmap should be especially useful to stakeholders internal and external to FDA as they seek support from OWH.

To foster transparency within and outside FDA, the Roadmap will be accessible on OWH's Women's Health Research website, where OWH makes a variety of information available on OWH activities, including on research projects and on funding.[43]

43 See *http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/default.htm*. Accessed October 2015.

FDA Office of Women's Health
www.fda.gov/womenshealthresearch